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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/336,036	06/18/99	SCHLIEVERT	P 600.347USI1

EXAMINER	
HINES, I	
ART UNIT	**PAPER NUMBER**
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/336,036	Schlievert et al.
Examiner	**Art Unit**
Ja-Na Hines	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Mar 1, 2001

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1, 3-10, and 17 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1, 3-10, and 17 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Amendment Entry

1. Amendments have been entered as filed on March 1, 2001. Claims 2 and 11-16 were canceled. Claims 1, 3-5, 7, 9 and 17 have been amended. Claims 17-19 are newly added. Claims 1, 3-10 and 17-19 are pending in this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 3-10 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a Streptococcal pyrogenic exotoxin type C (SPE-C) mutant with the specifically named amino acid substitutions in a Beta barrel of the B-subunit or a N-terminal alpha helix, does not reasonably provide enablement for a Streptococcal pyrogenic exotoxin type C (SPE-C) mutant with any amino acid substitutions in the Beta barrel of the B-subunit or a N-terminal alpha helix, whereby the amino acid sequence is altered by any substitution of one more amino acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claim 1 recites that the mutant can be obtained by any substitution of one or more amino acids in the Beta-barrel or N-terminal alpha helix, however that specification only provides guidance to specific amino acids and does not teach any amino acid substitution may be changed without causing a detrimental effect to the SPE-C toxin to be produced. The claim broadly recites an amino acid substitution, therefore any amino acid is being claimed, and no specific substitution is recited, if all the amino acids are substituted the resulting mutant SPE-C could result in a mutant toxin not taught or enabled by the specification.

Claim 19 recites that the mutant can be obtained by substituting one to six amino acids at positions 12, 15, 17, 35 or 38, however the claims does not teach what the amino acids can be substituted with. Further, the claims do not recite whether the substitution needs to be a conservative substitution. The specification only provides guidance to specific amino acids and does not teach any amino acid substitution may be changed without causing a detrimental effect to the SPE-C toxin to be produced even though the positions are recited. The claim broadly recites an amino acid substitution, therefore any amino acid is being claimed, and no specific substitution is recited, if all the amino acids at the recited positions are substituted the resulting mutant SPE-C could result in a mutant toxin not taught or enabled by the specification.

Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984", (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes:

1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge;

2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Proline residue, which must distort the alpha-helix;

3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "Protein structure: A Practical Approach, 1989; pages 184-186" teaches that present day site directed mutagenesis of a gene allows any amino acid in a protein sequence to be changed to any other, as well as introducing deletions and insertions. The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph) adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

The substitution of any amino acid in the recited location within the mutant SPE-C would not predictably result in a stable molecule. The specification only teaches the use of specific amino acids in specific locations which result in stable variations. No working examples are shown containing the missing information. Without such information, one of skill in the art could

not predict which deletions, substitutions or insertions or any combination thereof would result in the desired stable, active protein. Accordingly, one of skill in the art would be required to perform undue experimentation to use any amino acid at any location to produce a stable SPE-C toxin. Therefore, one skilled in the art could not make and/or use the invention without undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Goshorn et al., in view of Hartwig et al. Goshorn et al., teaches the nucleotide sequence of Streptococcal Pyrogenic Exotoxin type C and found that the SPE-C had the greatest sequence homology with SPE-A (abstract). SPE-C is a member of a family of biologically and biochemically related toxins produced by *Streptococcus pyogenes* and *Staphylococcus aureus* (page 2518). The toxins occur in three serologically distinct forms, A, B and C and have been associated with streptococcal toxic shock-like diseases (page 2518). The authors have also previously reported the cloning of the gene for SPE-C where the gene was localized, DNA fragments were ligated to bacteriophages, transformed in *E. coli* and recombinant phages were selected (page 2518). Deletion subclones

were obtained using exonuclease activity and further suggest using site-directed mutagenesis to analyze the toxin (page 2518). The SPE-C amino acid sequence was found to be highly related to SPE-A sequences and found to have a high degree of similarity by allowing conservative amino acids changes (page 2519, Table 1 and Figure 2). The amino acid alignments reveal some clusters of conservation particularly in the carboxyl halves of the proteins, however the regions may represent biologically important sites necessary for the structural integrity of the proteins (page 2519). However, Goshorn does not teach specific amino acid changes in the beta barrel of the B-subunit or the N-terminal alpha helix.

Hartwig et al., teaches streptococcal pyrogenic exotoxin A (SPEA) is an important pathogenicity factor of group A streptococci and it is a member of the family of super antigens (abstract). The authors have generated nine mutant SPEA molecules by substituting amino acids in the regions of homology between different streptococcal and staphylococcal superantigens (abstract). The N-terminal regions are important interaction with the TCR and with the MHC class II molecule (page 869). Several mutations lead to loss of function but does not effect binding of neutralizing antibodies (page 869). Introduction of point mutations changed the amino acids into alanines (page 870). Additional mutants were also created by deletion of the 10 N-terminal amino acids (abstract). Several mutations created lead to loss of function but do not affect the binding of neutralization antibodies (page 869). The Methods section teaches introduction of single point mutations into the speA gene and the expression and purification of the recombinant SPEA proteins and assays for mitogenic activity of mutants (page 870). Figure 1

shows the location of amino acids substitutions in the different mutants of SPEA. Figure 3 shows the mitogenic activity of mutant SPEA molecules. Some of the results show that the replacement of amino acid residues within the conserved regions of SPEA does not affect the expression of two individual neutralizing epitopes (page 874). Other studies using mutagenesis of toxin genes had been published, where some have substituted with cysteine or alanine (page 874). The residue Lys-138 is not part of the alpha5 groove and therefore is not directly involved in the class II interaction. The mutants are still able to induce such neutralizing antibodies and could be used for vaccination purposes (page 875).

Therefore, it would have been obvious at the time of applicants invention to have used the SPE-C which has the greatest sequence homology with SPE-A as taught by Goshorn et al., with the mutations and vectors taught by Hartwig et al., because Hartwig et al., teaches mutant SPE molecules by substituting and deleting amino acids where several mutations created lead to loss of function but do not affect the binding of neutralization antibodies.

Response to Arguments

4. Applicant's arguments filed March 1, 2001 have been fully considered but they are not persuasive.

5. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Goshorn et al., in view of Hartwig et al. In response to applicant's argument that there is no suggestion to combine the references because Goshorn et al., teaches the wild-type SPE-C and Hartwig et al., is drawn

to SPE-A, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it would have been obvious at the time of applicants invention to have used the SPE-C which has the greatest sequence homology with SPE-A as taught by Goshorn et al., with the mutations and vectors taught by Hartwig et al., because Hartwig et al., adding mutations within the N terminal region and teaches making mutant SPE molecules by substituting and deleting amino acids where several mutations created lead to loss of function but do not affect the binding of neutralization antibodies.

Withdrawn Rejections

6. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Streptococcal pyrogenic exotoxin type C (SPE-C), does not reasonably provide enablement for altering the amino acid sequence by any insertion, deletion or substitution of one more amino acid is withdrawn in view of applicants amendments.

7. Claims 1, 3-10 and 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicants amendments.

8. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Goshorn et al., is withdrawn in view of applicants amendments.

9. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goshorn et al., in view of Kline et al., is withdrawn in view of applicants amendments and declaration.

10. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goshorn et al., in view of Hartwig et al., is withdrawn in view of applicants amendments.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MEP. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines

May 12, 2001

JENNIFER E. GRASER
PRIMARY EXAMINER